



Review Article

Management of rhabdomyolysis: A practice management guideline from the Eastern Association for the Surgery of Trauma

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ABSTRACT

Background: The treatment of rhabdomyolysis remains controversial. Although there is no question that any associated compartment syndrome needs to be identified and released, debate persists regarding the benefit of further therapy including aggressive intravenous fluid resuscitation (IVFR), urine alkalization with bicarbonate, and the use of mannitol. The goal of this practice management guideline was to evaluate the effects of bicarbonate, mannitol, and aggressive intravenous fluids on patients with rhabdomyolysis.

Methods: A systematic review and meta-analysis comparing treatments in patients with rhabdomyolysis was performed. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was applied to assess the quality of evidence and to create evidence-based recommendations regarding the use of bicarbonate, mannitol, and aggressive IVFR in patients with rhabdomyolysis.

Results: A total of 12 studies were identified for analysis. On quantitative analysis, IVFR decreased the incidence of acute renal failure (ARF) and need for dialysis in patients with rhabdomyolysis. Neither bicarbonate nor mannitol administration improved the incidence of acute renal failure and need for dialysis in patients with rhabdomyolysis. Quality of evidence was deemed to be very low, with the vast majority of the literature being retrospective studies.

Conclusion: In patients with rhabdomyolysis, we conditionally recommend for aggressive IVFR to improve outcomes of ARF and lessen the need for dialysis. We conditionally recommend against treatment with bicarbonate or mannitol in patients with rhabdomyolysis.

1. Level of evidence

Guideline; Systematic review/meta-analysis, level IV.

2. Introduction

Rhabdomyolysis is a clinical syndrome characterized by skeletal muscle destruction and release of intracellular muscle contents into the bloodstream, causing systemic complications. Trauma is a leading cause

of rhabdomyolysis and can present in several forms including direct trauma, compression, and prolonged immobilization. Patients can present with rhabdomyolysis after crush injuries and entrapments, but may also follow more subtle presentations with exertion, medications and toxins. The term “crush syndrome” was first used by Bywaters in 1941 to describe muscle necrosis and a brown pigment in the urine seen in autopsy of renal tubules in patients buried several hours after a bomb attack in London.¹ Additional causes of rhabdomyolysis include drugs and toxins, marked exertion, infection, electrolyte disorders, and

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idiopathic etiologies.² The syndrome is characterized by muscle pain, weakness, dark tea colored urine, and marked elevations of serum creatine kinase (CK) levels. There is no universal definition of rhabdomyolysis, though often used definitions include CK levels 5 times above normal. The most common systemic complication of rhabdomyolysis is the development of acute renal failure (ARF). We chose the term ARF rather than the more recent classification of Acute Kidney Injury (AKI) given the older timeframe of most of the included studies.³

ARF is felt to occur through several mechanisms. These include hypovolemia from fluid sequestration in the extracellular space and toxic effects of myoglobin on the nephron both directly and through its breakdown products, such as free iron.⁴ Myoglobin itself has three mechanisms of renal toxicity through renal vasoconstriction, formation of intra-tubular casts, and direct toxicity of myoglobin to kidney tubular cells.⁵

The most important principle in the management of rhabdomyolysis is the identification and release of any causative compartment syndrome. The treatment for rhabdomyolysis otherwise remains controversial with respect to the amount of intravenous fluid resuscitation (IVFR) and the use of additional medical therapies such as bicarbonate and mannitol. The general goals in preventing myoglobin-induced ARF are to improve renal blood flow to minimize ischemia, increase urine flow rate to wash out obstructing casts, minimize the cytotoxic effects of myoglobin, and relieve any ongoing muscle compression such as compartment syndrome. IVFR works to restore renal perfusion and increase urine flow rate.⁵ In entrapped victims with crush syndrome and possible rhabdomyolysis, the Renal Disaster Relief Task Force of the International Society of Nephrology recommends starting intravenous saline prior to extraction at a rate of 1000 mL/h, with a goal of administering 3–6 L of fluids over the first day.⁶ Other protocols include consideration of bicarbonate therapy to alkalinize the urine by maintaining urinary pH > 6.5, mannitol administration if there is no anuria, and up to 12 L of IVF per day with a goal urine flow of 300 mL/h until myoglobin has cleared from the urine.⁷ On the other hand, consensus recommendations from Intensive Care Medicine in 2010 suggest that sodium bicarbonate is not necessary and not superior to saline diuresis.⁸ These recommendations were based on only one study, which we have included in our review.⁹ The evidence to support these recommendations is quite limited, consisting of small cases series and case reports. To better guide treatment of patients and identify areas for future research, the Eastern Association for the Surgery of Trauma (EAST) Practice Management Guidelines (PMG) Committee aimed to formulate recommendations regarding the use of IVFR, bicarbonate, and mannitol in the treatment of patients with rhabdomyolysis.

3. Objectives

The objective of this review was to evaluate outcomes in patients with rhabdomyolysis who had treatment with bicarbonate, mannitol, or aggressive IVFR compared with routine medical care. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was utilized to assess the level of existing evidence and create recommendations.¹⁰ The working group consisted of EAST members and one nephrologist (SA). The working group performed a systematic review and meta-analysis of the relevant clinical studies.

The following PICO (Population, Intervention, Comparison, Outcomes) questions were defined prior to literature search and systematic reviews:

3.1. PICO 1

In patients with rhabdomyolysis (P), should treatment with **bicarbonate** infusion (I) versus routine medical management without bicarbonate infusion (C) be utilized to improve the incidence of ARF and need for dialysis (O)?

3.2. PICO 2

In patients with rhabdomyolysis (P), should treatment with **mannitol** infusion (I) versus routine medical management without mannitol (C) be utilized to improve the incidence of ARF and need for dialysis (O)?

3.3. PICO 3

In patients with rhabdomyolysis (P), should **aggressive IVFR be used to achieve urine output of 2 mL/kg/hr** (I) versus routine medical management without aggressive IVFR (C) be utilized to improve the incidence of ARF, need for dialysis, and respiratory failure/pulmonary edema (O)?

Workgroup members chose to define aggressive IVFR as IVFR to achieve urine output of 2 mL/kg/hr as this seemed to reflect the concept of aggressive replenishment beyond our usual resuscitation goals of 0.5 mL/kg/hr. This was done prior to our literature search.

4. Outcome measure type

The outcomes were proposed and independently rated by each group member on a scale from 1 to 9, and the mean score for each outcome was calculated and assigned as the final score. Workgroup members proposed 5 outcomes for each PICO question, with 2 additional outcomes for PICO 3 (Table 1). Outcomes with rounded average scores 7–9 were deemed critical, scores of 4–6 were important outcomes, and those with scores of 1–3 were considered least important. Only critical outcomes were extracted and utilized for analysis.

The critical outcomes included development of acute renal failure and need for dialysis. Importantly, the definition of ARF is not consistent across studies. This inconsistency is well recognized across the literature for ARF.³ For the studies included in this analysis, ARF was defined by urine output (from as low as less than 200 cc/day to as high as less than 25 cc/hr) or creatinine increase (from as low as 1.5 times baseline to as high as 3 times baseline). Given the known association between aggressive IVFR and respiratory failure/pulmonary edema and compartment syndrome, these additional outcomes were also considered for PICO 3. Development of compartment syndrome as a result of IVFR was not reported in any studies, so this outcome was excluded from analysis.

5. Identification of REFERENCES

A professional medical librarian (HK) performed a search of citations in the following databases: PubMed, Embase, Cochrane Library, Web of Science, and Ovid Medline. The search was performed using the following MeSH terms: “rhabdomyolysis”, “bicarbonate”, “mannitol”, “fluid therapy”, and “infusions, intravenous”; the additional free-text terms, “traumatic rhabdomyolysis”, “fluid resuscitation”, and “aggressive fluid” were combined with the MeSH terms to obtain the citation

Table 1
Relevant Outcomes and work group ratings.

Outcome	PICO 1 Bicarbonate Mean rating	PICO 2 Mannitol Mean rating	PICO 3 IVFR Mean rating
Acute Renal Failure	7.75	7.75	7.5
Need For Dialysis	8.25	8.25	8.25
Intensive Care Length of Stay	6.25	6.25	5.875
Hospital Length of Stay	5.125	5.125	4.875
Duration of Dialysis/renal recovery	6.375	6.375	6.125
Respiratory Failure			7
Compartment Syndrome			6.625

results. The time period search was from January 1, 1946 to November 1, 2020. In addition, a hand search of bibliographies and recent review articles was also completed.

There were few studies in the literature so we chose to include suitable studies in non-traumatic or mixed populations of rhabdomyolysis and some pediatric series. Review articles, meta-analyses, case reports, and non-English language publications were excluded.

Each title and each abstract were screened independently by two members of the working group, with irrelevant studies then discarded. Then, the full texts of the remaining articles were independently screened by two independent working group members. Selected studies were included for final data extraction and analysis. All conflicts were adjudicated by a third reviewer/arbitrator (Fig. 1- PRISMA).

6. Data extraction and methodology

A total of 12 studies were included. Extracted data were entered into a Microsoft Excel 2013 (Redmond, WA, USA) spreadsheet. Data

extraction was done independently by two reviewers, with discrepancies adjudicated by a third blinded reviewer. Extracted data were meta-analyzed with mixed random-effect modeling in Review Manager (RevMan) software Version 5.3 (The Cochrane Collaboration, London, United Kingdom) and forest plots generated for each critical outcome. Dichotomous outcomes were reported as Risk Ratio (RR), and continuous variables were reported as Standardized Mean Difference (SMD). Confidence interval (CI) of 95% was presented with RR and SMD. Heterogeneity was calculated and quantified with I^2 . Outcomes with I^2 values less than 50% were defined to have a low degree of heterogeneity, those with I^2 values of 50–74% were defined as having moderate heterogeneity, and outcomes with I^2 values $> 75\%$ were indicative of high heterogeneity (reference Cochrane Handbook for Systematic Reviews of Interventions).

7. Grading the evidence

Consensus on the quality of analyzed literature was reached for each

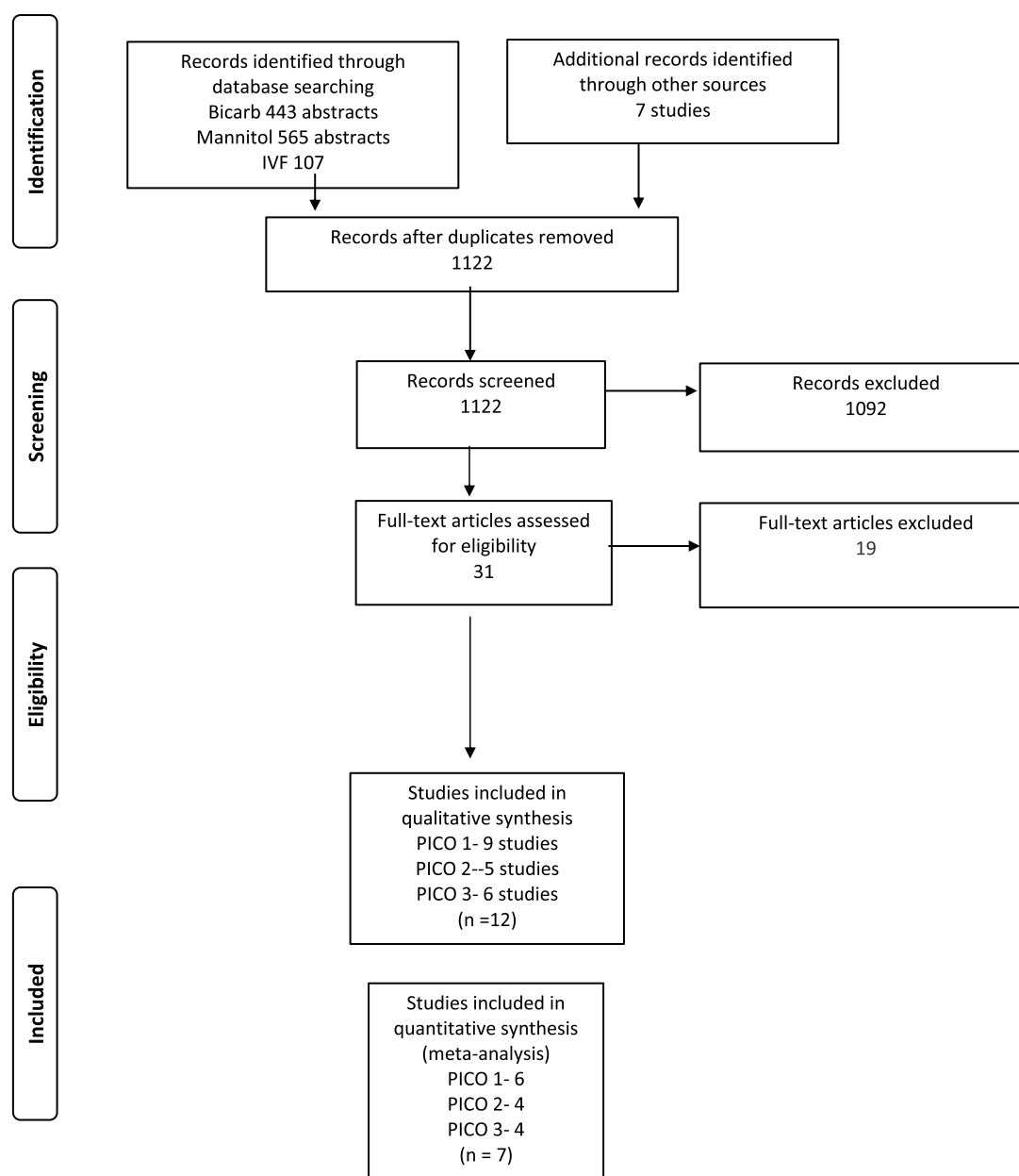


Fig. 1. Prisma.

PICO question. Parameters taken into consideration included: risk of bias; inconsistency; indirectness; imprecision; and publication bias. The overall quality of evidence was then calculated to be high, moderate, low or very low, using GRADEpro GDT (Guideline Development Tool) software (McMaster University, 2014).¹⁰ Based on the results of the meta-analyses and the evidence quality, all members of the committee then voted on recommendations for each PICO question, taking additionally into consideration the relationship of benefits and harms, patient values and preferences, and resource utilization.

8. Results for the use of bicarbonate (PICO 1)

In patients with rhabdomyolysis (P), should treatment with **bicarbonate** infusion (I) versus routine medical management without bicarbonate infusion (C) be utilized to improve the incidence of ARF and need for dialysis (O)?

9. Qualitative analysis

A total of nine studies were selected to answer PICO 1; all were retrospective cohort studies.^{9,11–18} Most studies evaluated predominately trauma patients, three studies reported on crush injuries after earthquake/building collapse, and one study contained predominately medical patients secondary to overdose. Importantly, there was no standardized way that bicarbonate was administered across the studies; most had a standardized approach to fluid resuscitation, including alkalization of the urine with bicarbonate and the use of mannitol.¹³ In some series bicarbonate was administered based on physician discretion.^{9,18} One series included acetazolamide administration with bicarbonate in the treatment group.¹³ Some of the studies had contrasting conclusions. The largest series by Brown et al. included 382 trauma patients with CK > 5000 U/L admitted to the ICU. Of these, 154 received combined bicarbonate/mannitol therapy per treatment algorithm and 228 did not; this was based on physician discretion. This study revealed no difference in ARF, need for dialysis, or mortality between the patients that received bicarbonate/mannitol therapy and those that did not.⁹ In another study by Nielsen et al. of 56 trauma patients with CK > 10,000 U/L, 46 were treated by a protocol that included fluid resuscitation, bicarbonate, and mannitol were compared with ten patients not treated with this protocol. This group found that ARF occurred in 26% of patients with this protocol and 70% without the protocol ($P = .008$).¹⁴

10. Quantitative analysis (meta-analysis)

Six of the studies had a comparator group and reported relevant outcomes, thus were suitable for meta-analysis. There was no difference in the incidence of ARF between groups that were treated with bicarbonate versus those that did not (RR 0.93, CI 0.39–2.22). Similarly, there was no difference in need for dialysis between groups across 5 studies with 498 patients (RR 0.38, CI 0.07–2.11) Fig. 2a and 2b.

11. Grading the evidence

The evidence was assessed applying the GRADE framework (Table 2a). First, the quality of evidence was lowered for all outcomes due to the inclusion of observational studies and the high risk of selection bias across these. We also downgraded the level of evidence for inconsistency due to overlapping effects when combining bicarbonate with other interventions, and because of a wide range of results. The low number of included studies, low number of subjects, and wide confidence intervals led to downgrading the level of evidence for imprecision for each of the outcomes. Overall, the level of evidence was assessed to be very low.

12. Recommendation for the use of bicarbonate (PICO 1)

Based on the analysis of included studies, the effect of bicarbonate on the selected outcomes, and the very low level of evidence; **we conditionally recommend against** the use of bicarbonate in patients with rhabdomyolysis versus routine medical care without bicarbonate to improve outcomes of ARF or need for dialysis. Five workgroup members felt a conditional recommendation against bicarbonate use should be made. Three members felt that no recommendation could be made for or against the use of bicarbonate due to inconsistency of results including some studies that suggested benefit to bicarbonate use.

13. Results for the use of mannitol (PICO 2)

In patients with rhabdomyolysis (P), should treatment with **mannitol** infusion (I) versus routine medical management without mannitol (C) be utilized to improve the incidence of ARF and need for dialysis (O)?

14. Qualitative analysis

Our search yielded a total of six studies, all of which were retrospective cohort or case series.^{9,11,12,14,15,18} All six also included bicarbonate treatment and were included in PICO 1 with patients receiving both bicarbonate and mannitol. The dose of mannitol was not standardized and ranged from bolus administration of 0.5 gm/kg to infusions of 1–2 gm/kg over 4 h. Most studies commented on making sure the patient was adequately volume resuscitated before starting treatment with mannitol. The results in the literature include the same two largest studies as in the bicarbonate discussion above, where treatment with bicarbonate and mannitol was combined yielding conflicting results. Importantly, a recent meta-analysis demonstrated intravascular mannitol did not convey any additional benefit beyond adequate hydration in patients at increased risk for AKI, and for contrast induced nephropathy the use of mannitol was detrimental.¹⁹

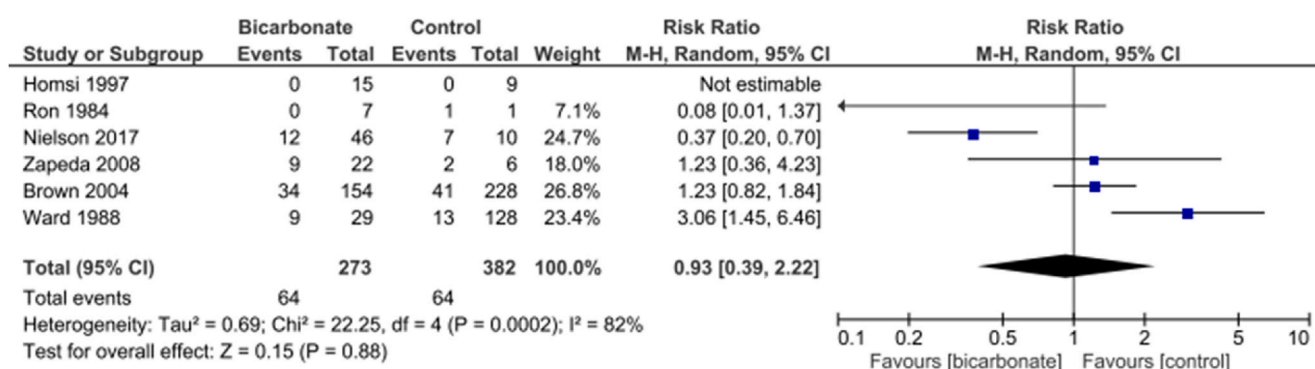


Fig. 2a. Forest Plot PICO 1 Bicarbonate outcome ARF.

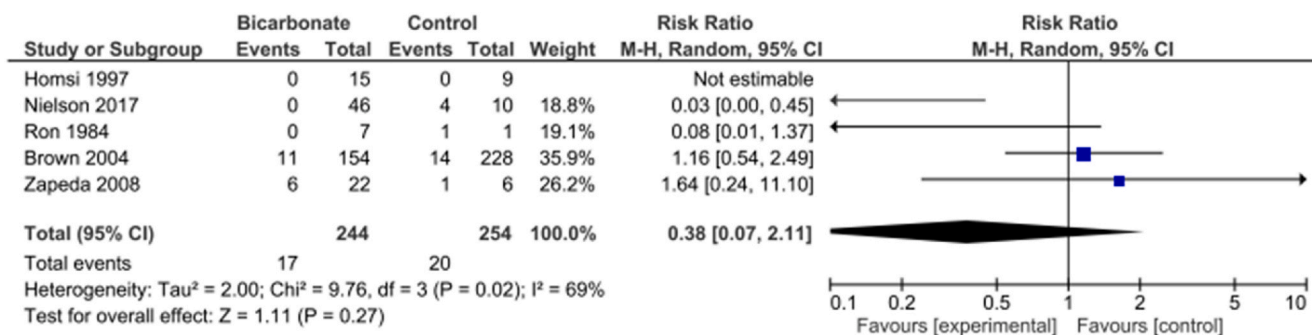


Fig. 2b. Forest Plot PICO 1 Bicarbonate outcome Dialysis.

Table 2(a)

GRADEpro evidence profile table for bicarbonate **Question:** Bicarbonate compared to usual care for Rhabdomyolysis.**Question:** Bicarbonate compared to usual care for Rhabdomyolysis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bicarbonate	usual care	Relative (95% CI)	Absolute (95% CI)		
acute renal failure												
6	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	64/273 (23.4%)	64/382 (16.8%)	RR 0.930 (0.039 to 2.220)	12 fewer per 1,000 (from 161 fewer to 204 more)	⊕○○○○ VERY LOW	CRITICAL
Need for dialysis												
5	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	17/244 (7.0%)	20/254 (7.9%)	RR 0.38 (0.07 to 2.11)	49 fewer per 1,000 (from 73 fewer to 87 more)	⊕○○○○ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

- a. retrospective, selection bias
- b. heterogeneous results
- c. variable patient population
- d. small numbers, wide CI

15. Quantitative analysis (meta-analysis)

Four of the studies had a comparator group and reported relevant outcomes and thus were suitable for meta-analysis. There was no difference in the incidence of ARF between groups in treatment with mannitol versus no mannitol in 577 total patients (RR 0.71, CI

0.31–1.61). Similarly, there was no difference in need for dialysis between groups in 446 patients over 3 studies (RR 0.18, CI 0.01–2.51) Fig. 3.

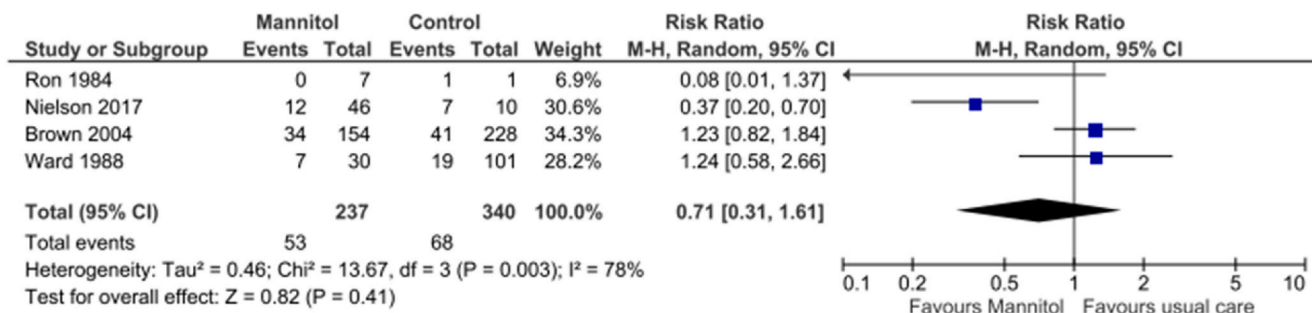


Fig. 3a. Forest Plot PICO 2 Mannitol outcome ARF.

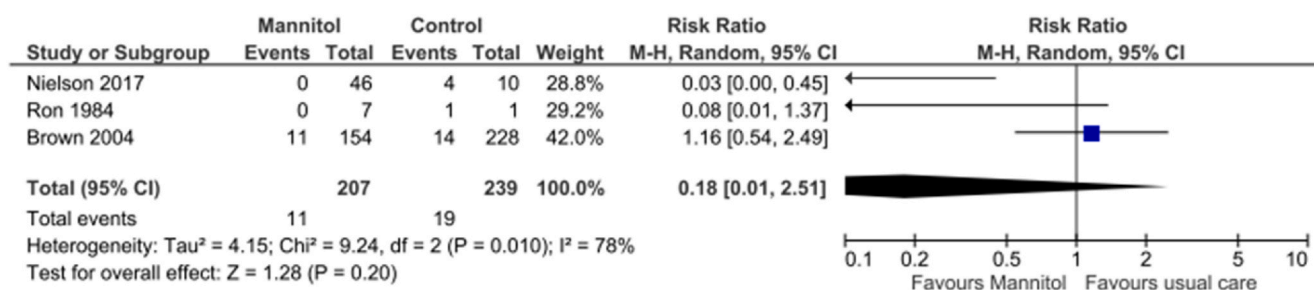


Fig. 3b. Forest Plot PICO 2 Mannitol outcome Dialysis.

16. Grading the evidence

The evidence was assessed applying the GRADE framework (Table 2b). First, the level of evidence was decreased for all outcomes due to the inclusion of observational studies, given the high risk of selection bias across these. We downgraded the level of evidence further for inconsistency due to overlapping effects when mannitol was combined with other interventions and for a wide range of results. The low number of included studies, low number of subjects, and wide confidence intervals led to downgrading the level of evidence for imprecision for each outcome. Overall, the level of evidence was assessed to be very low.

17. Recommendation for the use of mannitol (PICO 2)

Based on the available evidence, the effect of mannitol on the selected outcomes, and the very low level of evidence; **we conditionally recommend against** the use of mannitol in patients with rhabdomyolysis versus routine medical care without mannitol to improve outcomes of ARF or need for dialysis. Six workgroup members felt that since the quality of evidence was lower and potential for harm higher for

mannitol than bicarbonate, a conditional recommendation against the use of mannitol was most appropriate. Two members felt that due to conflicting results no recommendation could be made for or against the use of mannitol.

18. Results for the use of aggressive intravenous fluids (PICO 3)

In patients with rhabdomyolysis (P), should **aggressive IVFR be used to achieve urine output of 2 mL/kg/hr (I)** versus routine medical management without aggressive IVFR (C) be utilized to improve the incidence of ARF, need for dialysis, and respiratory failure/pulmonary edema (O)?

19. Qualitative analysis

Our search yielded a total of ten studies, nine of which were retrospective cohort or case series.^{11,12,14,15,20–23} There was one prospective, randomized study comparing normal saline versus lactated ringers for treatment of rhabdomyolysis secondary to doxylamine intoxication.²⁴ Most studies included vigorous IVFR, but the amounts were variably reported as 400 mL/h,²⁴ 4–8 L/day,¹¹ averaging 568 mL/h over first 2.5

Table 2(b)

GRADEpro evidence profile table for Mannitol **Question:** Mannitol compared to usual care for Rhabdomyolysis.

Question: Mannitol compared to usual care for Rhabdomyolysis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mannitol	usual care	Relative (95% CI)	Absolute (95% CI)		
Acute Renal Failure												
3	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	53/237 (22.4%)	68/340 (20.0%)	RR 0.71 (0.31 to 1.61)	58 fewer per 1,000 (from 138 fewer to 122 more)	 VERY LOW	CRITICAL
Need for Dialysis												
3	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	11/207 (5.3%)	19/239 (7.9%)	RR 0.18 (0.01 to 2.51)	65 fewer per 1,000 (from 79 fewer to 120 more)	 VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

- a. retrospective, selection bias
- b. heterogeneous results
- c. variable patient population
- d. small numbers, wide CI

days¹⁵ and using bolus administration protocols.^{12,14} One pediatric series included 28 patients of whom ten received a fluid bolus in the first day of 20 cc/kg of saline.²¹ Studies did not report hourly urine output which was part of our defined intervention, but some of the protocols included goal urine output ranges from 2 to 3 mL/kg/hr¹⁴ to 300 mL/h.¹⁵ Overall, the studies had mixed patient populations and interventions making it difficult to interpret the results of treatment with intravenous fluids. Additional outcomes of development of respiratory failure/pulmonary edema were not consistently reported in the studies and excluded.

20. Quantitative analysis (meta-analysis)

Four of the studies had comparator groups suitable for meta-analysis. In one series the authors did not use a rhabdomyolysis protocol in patients with CK between 10,000 and 20,000 U/L for a period of time, allowing a comparison group to patients that were treated with this protocol that included fluids, bicarbonate, and mannitol.¹⁴ In the second study, there was a patient where the diagnosis of rhabdomyolysis was delayed and therefore not treated, allowing comparison with those who did undergo treatment.¹⁵ In the third pediatric series, ten of 28 patients received a fluid bolus and had outcomes of dialysis reported.²¹ A final study included 14 crush syndrome patients after an earthquake in Japan. Some of the patients presented in a delayed fashion allowing comparison of six patients that received low volume of IVF (less than 100 mL/h) versus eight patients that received more than this amount and were classified as high volume IVF.²⁵ The quantitative analysis did reveal lower rates of ARF in patients receiving IVFR in four patients across two studies, (RR 0.33, CI 0.14–0.77). Similarly, there was a lower need for dialysis in patients receiving IVFR for 106 patients across four studies (RR 0.21, CI 0.06–0.72) Fig. 4.

21. Grading the evidence

The evidence was assessed applying the GRADE framework (Table 2c). First, the level of evidence was decreased for all outcomes due to the inclusion of overwhelmingly observational studies. The risk for selection bias was high across these studies. We also downgraded the level of evidence for inconsistency due to overlapping effects with combining intravenous fluids with other interventions and due to widely ranging results. Also, the amount of fluids administered and monitoring of response was not standardized. The low number of included studies, low number of subjects, and wide confidence intervals led to downgrading the level of evidence for imprecision for all outcomes. Overall, the level of evidence was assessed as very low.

22. Recommendation for the use of aggressive intravenous fluid resuscitation (PICO 3)

Based on the analysis of included studies, the effect of IV fluids on the selected outcomes, and the very low level of evidence, we conditionally recommend for the use of aggressive IVFR in patients with rhabdomyolysis, versus usual medical care, to improve outcomes of ARF or

need for dialysis. Although IVFR in rhabdomyolysis is well established, the amount of volume to administer and response to resuscitation are variable in the studies reviewed, leading six workgroup members to make a conditional recommendation. Two members felt a strong recommendation for the use of aggressive IVF could be made. We support a UOP goal of 2–3 mL/kg/hr for patients undergoing IVFR which is in the middle range of published reports.^{5,14,26} We recommend continued treatment with IVFR until a predefined threshold is reached such as the CK levels downtrend below 5000–10,000 U/L or myoglobin is cleared from the urine.^{14,26} The patients entire clinical context including underlying medical comorbidities, associated injuries and other active hospital conditions needs to be considered in making these decisions.

23. Using these guidelines in clinical practice

The first principle in the treatment of rhabdomyolysis should be the identification and release of any causative compartment syndrome. This practice management guideline addressed the role of adjunctive bicarbonate, mannitol, and aggressive intravenous fluid administration in patients with this condition. After performing an extensive literature search and assessing the existing evidence, we conditionally recommend using aggressive IVFR in the management of patients with rhabdomyolysis. Because of the paucity of data and overlapping treatment effects, we are basing our recommendations on our collective judgment after interpreting the data. This is in accordance with GRADE methodology which requires subjective judgement when quality of evidence is very low while considering other factors such as patient and clinician values, the balance between desirable and undesirable effects, resources, and costs.²⁷ When making these treatment decisions, the entire clinical context of the patient needs to be considered including underlying comorbidities, associated injuries and response to treatment. We would recommend initiating treatment for CK levels greater than 5000–10,000 U/L as commonly used treatment thresholds.^{14,26} The amount of IVFR is not clearly defined by the studies, but we support rapid resuscitation and targeting higher urine output goals (upwards of 2–3 mL/kg/hr) in appropriate patients until CK is down trending. A recent review recommended starting with 1 L boluses and then titrating fluids to higher urine output goals.²⁸ We conditionally recommend against the use of bicarbonate or mannitol in patients with rhabdomyolysis, as no clear benefit was demonstrated in our meta-analysis, and there may be risks associated with these treatments (see mannitol section qualitative analysis above).¹⁹ Our recommendations are consistent with other recent review articles that also do not recommend treatment with bicarbonate or mannitol in patients with rhabdomyolysis.^{28,29} If bicarbonate and mannitol are to be used, we suggest that protocolized use tailored specifically for rhabdomyolysis be considered, such as described by Nielsen et al.¹⁴ We would further encourage publication of the results of this protocolized intervention to add the paucity of literature on this subject. Our recommendations are summarized in Table 3.

The workgroup felt that the main limitation in creating this guideline was the limited, poor quality evidence from which we made our recommendations. It was surprising that so few series have been reported

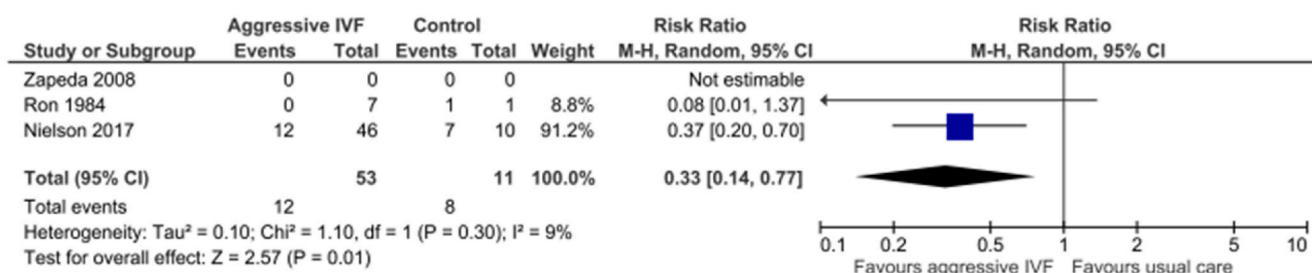


Fig. 4a. Forest Plot PICO 3- Intravenous fluid resuscitation (IVFR) outcome ARF.

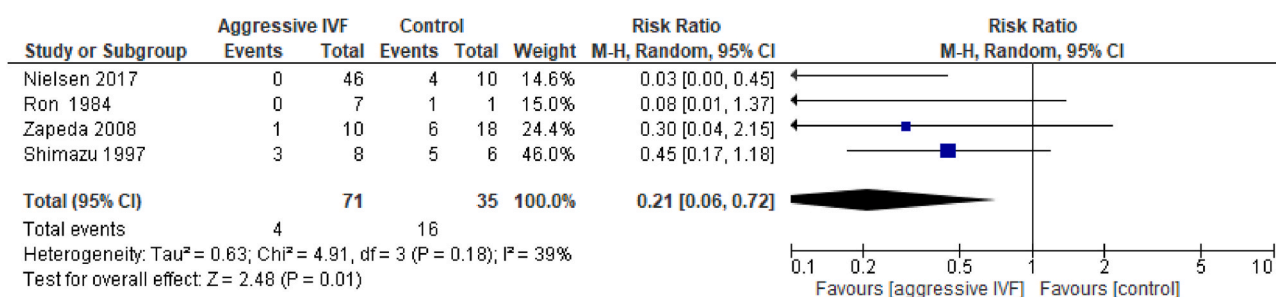


Fig. 4b. -Forest Plot PICO 3- Intravenous fluid resuscitation (IVFR) outcome Dialysis.

Table 2(c)

GRADEpro evidence profile table for Aggressive IVFR **Question:** Aggressive IVFR compared to usual care for Rhabdomyolysis.**Question:** Aggressive IVFR compared to usual care for Rhabdomyolysis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aggressive IVFR	usual care	Relative (95% CI)	Absolute (95% CI)		
Acute renal failure												
3	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	12/53 (22.6%)	8/11 (72.7%)	RR 0.33 (0.14 to 0.77)	487 fewer per 1,000 (from 625 fewer to 167 fewer)	⊕○○○ VERY LOW	CRITICAL
Need for Dialysis												
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aggressive IVFR	usual care	Relative (95% CI)	Absolute (95% CI)		
4	observational studies	serious ^a	serious ^b	serious ^c	serious ^d	none	4/71 (5.6%)	16/35 (45.7%)	RR 0.21 (0.06 to 0.72)	361 fewer per 1,000 (from 430 fewer to 128 fewer)	⊕○○○ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

- a. retrospective, selection bias
- b. heterogeneous results
- c. variable patient population
- d. small numbers, wide CI

Table 3

Summary of Recommendations for Patients with Rhabdomyolysis to improve outcomes of ARF and need for dialysis.

Intervention	Workgroup Recommendation
PICO 1- Use of Bicarbonate	Conditionally recommend against
PICO 2- Use of Mannitol	Conditionally recommend against
PICO 3- Use of aggressive IV fluid resuscitation	Conditionally recommend for (goal to achieve UOP of 2–3 mL/kg/hr while considering entire clinical context)

for the common clinical condition of rhabdomyolysis over the past 20 years. Given this limited data, the workgroup chose to include patients with mixed etiologies for rhabdomyolysis as well one series of pediatric

patients further contributing to the heterogeneity of results. Across the studies indications for initiation of dialysis were not reported or standardized. Further studies, ideally prospective, randomized, and multi-center, are needed to further clarify the amount and duration of IVFR needed, as well as the role for bicarbonate and mannitol in the treatment of rhabdomyolysis.

24. Conclusions

In patients with rhabdomyolysis, after identification and release of any causative compartment syndromes, we conditionally recommend aggressive IVFR over usual medical care to improve outcomes of ARF and need for dialysis. We conditionally recommend against treatment with bicarbonate or mannitol in these patients.

Authors' contribution

JS: study idea, study design, literature search, data collection, data analysis, data interpretation, drafting the manuscript.

AG: study design, data collection, data interpretation, and critical revisions.

SA: study design, data collection, data interpretation, and critical revisions.

CD: study design, data collection, data interpretation, and critical revisions.

NP: study design, data collection, data interpretation, and critical revisions.

MK: study design, data collection, data interpretation, and critical revisions.

GK: study design, data collection, data interpretation, and critical revisions.

JJC: study design, data collection, data interpretation, and critical revisions.

Declaration of competing interest

No authors report conflict of interests.

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